REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 27, 28, 30-33 and 36 are in the case.

I. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 1-36 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. In response, and without conceding to the rejection, claims 1-26 have been canceled without prejudice, thereby rendering moot the formal rejections of those claims. The amendments to claims 27-36 obviate the remaining formal points. Withdrawal of the formal rejection is respectfully requested.

II. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 1-12, 15-22 and 28-35 are rejected under 35 U.S.C. §112, first paragraph, because the specification while enabling for treating breast cancer, allegedly does not reasonably provide enablement for treating any or all cancers and solid tumors. In response, and without conceding to this rejection, claims 1 to 12 and 15 to 22 have been cancelled without prejudice. Claim 28 has been restricted to the use of the compound 3-ethyl-6-[3-(4-morpholinyl)propoxy]-1,2,4-benzotriazine 1,4-dioxide, and also incorporates the subject matter of original claim 29, which specifies that the tumor cells are in a hypoxic environment. Claim 29 has been canceled without prejudice.

By way of clarification regarding the mechanism of action, the compounds of the present invention are bioreductive drugs. These agents are prodrugs that are selectively activated by enzymatic reduction in hypoxic cells, resulting in formation of a

cytotoxin. Many human tumors contain a significant fraction of hypoxic cells. The presence of hypoxic cells arises because the extravascular transport of oxygen is compromised due to an inefficient microvascular system within the tumor. Reduction of oxygen tension in tumors leads to radioresistance.

Bioreductive prodrugs, including the compound of the amended claims, are targeted to the hypoxic regions in tumors. The compounds are therefore useful in the treatment of any type of cancer that contains hypoxia in situations where hypoxia limits available treatment options (such as radiation).

The presence of the target does not correlate closely with histiotype, and hypoxia is not present in every tumor. But the presence of the target can be discerned in principle, and increasingly in practice, using a variety of diagnostic tests. It is, therefore, not appropriate to focus narrowly on the tissue of origin as a way of classifying cancer in the modern era of individualized cancer medicine.

Attention is directed to the attached copy of a published paper J. Med. Chem. 2007, 50, 6654-6664 (Hay *et al.*) which provides data showing that the compound of the amended claims has *in vivo* activity against hypoxic cells in HT29 human tumor xenografts. The compound claimed in the present application is compound 22 shown in Figure 5 on page 6662. The compound 22 displayed approximately 3-fold greater log cell kill of hypoxic cells in HT29 tumors than the known compound tirapazamine (TPZ).

Attention is also directed to the attached copy of a signed Declaration by Professor William R. Wilson (the Wilson declaration), one of the inventors for this case. The data in the Wilson declaration shows that the compound of the amended claims (referred to as SN29751 in the Wilson declaration) has activity against hypoxic tumor

cells, in a variety of human tumor xenografts in nude mice, namely SiHa cervical carcinoma, HT29 colon carcinoma, H460 non small cell lung cancer and H1299 non small cell lung cancer. These results also show that SN29751 is less toxic than TPZ to mice and that at doses providing equivalent toxicity SN29751 has activity against hypoxic cells that is at least equal to TPZ and in most tumor models clearly superior to TPZ.

It appears from comments in the Action (in particular on page 5, third to last and final paragraphs, page 7 and the paragraph bridging pages 8 and 9) that the Office understands that the compounds of the present application inhibit cell proliferation by imparting cytotoxicity via hypoxia. This is not correct. As discussed above, the compounds are targeted to hypoxic regions in the tumor. The discussion of Bussink *et al.* (paragraph bridging pages 8 and 9 of the Action) relating to hypoxia inducing factor and protein kinase inhibitors is, therefore, irrelevant to the present application.

Claim 28 is now limited to the treatment of tumor cells in a hypoxic environment. A person skilled in the art would expect the compound to be useful to treat a wide range of human tumors having hypoxic regions. Withdrawal of the lack of enablement rejection is respectfully requested.

III. THE 35 U.S.C. §101 REJECTION

Claims 10, 11, 21, 22, 34 and 35 are rejected under 35 U.S.C. §101 because of the claimed recitation of a use. In response, claims 10, 11, 21, 22, 34 and 35 have been cancelled without prejudice. Withdrawal of this rejection is respectfully requested.

IV. THE ANTICIPATION REJECTIONS

Claims 1-25 and 27-36 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Lee *et al*. WO 89/08647. Claims 1-25 and 27-36 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lee *et al*. WO 91/004028. Claims 2, 3, 13, 14 and 27 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by DD 272 591. Claims 1, 2, 4-12, 13, 15-24 and 28-36 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Brown *et al*., EP 0649 658. Claims 1-25 and 27-36 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lee *et al*. US 20020103200. The rejections are respectfully traversed.

As noted above, claims 1-26 have been canceled without prejudice. Withdrawal of the anticipation rejections relating to those claims is respectfully requested.

With regard to the remaining claims, the cited references do not disclose the specific compound 3-ethyl-6-[3-(4-morpholinyl)propoxy]-1,2,4-benzotriazine 1,4-dioxide, to which the claims are now limited. Withdrawal of the anticipation rejections of claims 27-36 is respectfully requested.

V. THE OBVIOUSNESS REJECTIONS

Claims 1-36 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Lee *et al*., WO 89/08647. Claims 1-36 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Lee *et al*. US 20020103200 (or US 5,175,287). Claims 2, 3, 13, 14 and 24-27 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over DD 272 591. Claims 1-36 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown *et al*. WO 97/1 699. Claims 1-36 are rejected under 35 U.S.C.

§103(a) as allegedly unpatentable over Brown *et al.* EP 0649 658. The rejections are respectfully traversed.

WO 89/08647 (Lee '647) describes a method of selectively killing hypoxic tumour cells by administering a 1,2,4-benzotriazine oxide of a generic formula, which encompasses a very large number of compounds. However, Lee contains no suggestion that would have motivated a person of ordinary skill in the art to make that compound. The preparation of eight compounds is described in the examples of Lee '647. However, all of these compounds have significant structural differences from the compound claimed in the present application. The presently claimed compound has a 4-morpholinyl-3-propoxy group at the 6-position of the phenyl ring and an ethyl group at the 3-position of the triazine ring. None of the compounds disclosed in Lee '647 contains either an alkyl group, or even an ethyl group on its triazine ring, or a 4-morpholinyl-3-propoxy group on its benzene ring. In addition, Lee '647 provides cytotoxicity data on only one compound, 3-amino-1,2,4-benzotriazine 1,4-dioxide. This compound is also structurally very different to the compound as claimed in the present application.

A person skilled in the art would find no disclosure or suggestion in Lee '647 to modify the compounds specifically disclosed therein to arrive at the compound claimed in the present application. Lee '647 also contains a list of 138 particularly preferred compounds. The compounds most similar to those of the present application appear to be the compounds listed on page 10, lines 19 to 25, which contain a (2-hydroxy~3-morpholino) propoxy substituent on the benzene ring. However, these compounds have a hydroxy or an amino substituent on the triazine ring, rather than an ethyl group.

The specification does not include any data concerning the efficacy of these compounds. Lee '647 contains no disclosure or suggestion that would have motivated a person skilled in the art to modify these compounds by removing the hydroxy from the morpholino substituent and replacing the amino or hydroxy group on the triazine ring with an ethyl group, which is what would be required to arrive at the compound of the present application.

In light of the above, it is believed that the claimed invention is not rendered unpatentable by Lee '647. Withdrawal of the obviousness rejection based on that reference is respectfully requested.

WO 91/004028 (Lee *et al.*) (Lee '028), like Lee '647, describes a method of radiosensitising hypoxic tumour cells by administering a compound of a generic formula I, which includes a very large number of compounds. Lee '028 contains preparative examples for 15 compounds. None of these compounds is similar to the compound as claimed in the present application. None of the Lee '028 compounds has either an ethyl group on the triazine group or a 4-morpholinyl-3-propoxy group on the benzene ring. Cytotoxicity data is disclosed only for the compound 3-amino 1,2,4-benzotriazine 1,4-dioxide. Lee '028 contains no disclosure that would provide motivation to a person skilled in the art to modify the compounds disclosed therein to produce the compound as claimed in the present application.

In light of the above, it is believed that the claimed invention is not rendered unpatentable by Lee '028. Withdrawal of the obviousness rejection based on that reference is respectfully requested.

US 20020103200 (Lee et al.) (Lee '200) has a disclosure which is very similar to the disclosure of Lee '647 and Lee '028, discussed above. Accordingly, for the same reasons as those set out above, the present claims are not rendered unpatentable by Lee '200. Withdrawal of the obviousness rejection based on that reference is respectfully requested.

DD 272591 discloses herbicidal compounds. The compound of the present application does not fall within the scope of the generic formula described in DD 272591. The compounds described in DD 272591 all require an amino substituent on the triazine ring. The compound of the present application has an ethyl group in the same position, as well as a 4-morpholinyl-3-propoxy group on the benzene ring. The compounds of DD 272591 are therefore quite different to the compound of the present application. DD 272591 contains no suggestion to one of ordinary skill to modify the compounds disclosed therein to arrive at the compound as claimed in the present application. For these reasons, the claims of the present application are not rendered unpatentable over DD 272591. Withdrawal of the obviousness rejection based on that reference is respectfully requested.

WO 97/11699 (Brown et al.) (Brown '699) discloses an aqueous parenteral formulation for the treatment of cancer, comprising a compound of the generic formula I in a parenterally acceptable buffer. The formula I encompasses a very large number of compounds. However, the only examples of formulations given in the specification of Brown '699 contain the compound tirapazamine. Accordingly, Brown '699 contains no disclosure or suggestion to make the compound as claimed in the present application.

Withdrawal of the obviousness rejection based on that reference is respectfully requested.

Reference is also made to the Hay *et al.* reference discussed above (copy attached) which demonstrates that the compound of the present application has a 3-fold greater log cell kill of hypoxic cells in HT29 tumours than tirapazamine. The attached Wilson declaration also demonstrates the superiority of the present compound over TPZ. The presently claimed compound therefore has significantly superior properties over those of the sole compound disclosed in the formulations of Brown '699. For these further reasons, withdrawal of the obviousness rejection based on Brown '699 is in order and is requested.

EP 0649658 (Brown *et al.*) (Brown '658) describes a method of treating cancer by administering a compound of the general formula I in combination with a chemotherapy agent. The general formula I encompasses a very large number of compounds and, of the compounds of formula I specifically disclosed in the examples, compound 31 is similar to the compound of the present application. However, while this compound has an ethyl group on the triazine ring, the benzene ring is unsubstituted, in contrast to the compound of the present application, which contains a 4-morpholinyl-3-propoxy substituent. Brown '658 contains no disclosure or suggestion to modify the compound 31 to produce the compound of the present application. The amended claims are therefore not rendered unpatentable in view of Brown '658. Withdrawal of the obviousness rejection based on that reference is respectfully requested.

VI. INFORMATION DISCLOSURE STATEMENT

A Supplementary Search Report has recently issued on the corresponding European application. A copy is attached. The Supplementary Search Report cites references that were not cited in the International Search Report or by the USPTO. These are listed in an Information Disclosure Statement presented herewith, along with the requisite IDS fee. Entry is respectfully requested.

VII. AMENDMENTS

The amended claims are based on current claims 27 to 33 and 36, but are restricted to the compound 3-ethyl-6-[3-(4-morpholinyl)propoxy]-l ,2,4-benzotriazine 1,4-dioxide and its pharmacologically acceptable salts. Claims 1 to 26 and 29 have been cancelled without prejudice. The specification has been amended to include a customary heading and a new Abstract is presented. No new matter is entered.

Favorable action is awaited.

Respectfully submitted,

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Attachments: Declaration by Professor William R. Wilson; IDS including Supplementary Search Report; Hay *et al.*; USP 4,027,022, USP 3,991,189; 5,175,287; WO 2004/026846; Shinde *et al.*; IDS fee